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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/680,449	10/06/2003	Liwen Huang	1438.01	4490
26698	7590	05/15/2007	EXAMINER	
MYRIAD GENETICS INC.			WOLLENBERGER, LOUIS V	
INTELLECTUAL PROPERTY DEPARTMENT			ART UNIT	PAPER NUMBER
320 WAKARA WAY			1635	
SALT LAKE CITY, UT 84108				
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/680,449	HUANG ET AL.	
	Examiner	Art Unit	
	Louis V. Wollenberger	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 22 March 2007.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-34 is/are pending in the application.
 - 4a) Of the above claim(s) 1-15 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 16-34 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of Application

Applicant's response filed 22 March 2007 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 22 November 2006 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

With entry of the amendment filed on 22 March 2007, Claims 1–34 are pending. Claims 1–15 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claim Rejections - 35 USC § 112, second paragraph—new

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 16–29 and 31–33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

MPEP §2173 states in part that “The primary purpose of this requirement of definiteness of claim language is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent.”

In the instant case the claimed kits require the construction and use of a “chimeric RNA transcript.” Neither the claims nor the specification define the term “chimeric RNA transcript” in a manner that would clearly inform one of skill in the art as to which polynucleotide sequences are specifically included and/or excluded by the claimed kits. Thus, the metes and bounds of the claims are unclear. While the specification defines the term “chimeric RNA transcript” at page 16 as an RNA transcript comprising a subject RNA operably linked to a universal target RNA to create a single RNA that does not naturally occur in nature (page 16, bottom). This definition without more does not adequately distinguish the nearly countless numbers of naturally occurring ribopolynucleotide sequences from the virtually limitless number of potential non-naturally occurring and undefined sequences contemplated by applicants for use in the instant claims. One of skill presented with a ribopolynucleotide sequence (RNA) would not know *a priori* based on the sequence alone whether that sequence and others like it sharing common or redundant core sequences does or does not fall within the scope of the instant claim. The Application provides no guidance beyond the definition at page 16 as to how to unambiguously determine whether any given two or more RNAs do or do not occur in nature.

Accordingly, the instant claims are rejected for failing particularly point out and distinctly claim the invention.

Claim Rejections - 35 USC § 112, first paragraph—new

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16–29 and 31–33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, complete or partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient.

The claims are drawn to a kit comprising a plurality of expression vectors, cells, or organisms, each comprising an expression cassette that directs the expression of a chimeric RNA transcript that has a subject RNA operably linked to a universal target RNA, wherein at least two of the plurality of expression vectors, cells, or non-human organisms express chimeric RNA transcripts with different subject RNAs, and wherein all of said plurality of expression vectors, cells, or organisms express chimeric RNA transcripts with the same universal target RNA; and a

universal interfering RNA targeting said universal target RNA, or an interfering RNA transcription vector that directs the expression of said universal interfering RNA, wherein said universal interfering RNA is an siRNA or shRNA.

The specification defines a “chimeric RNA transcript” as an RNA transcript comprising a subject RNA operably linked to a universal target RNA to create a single RNA that does not naturally occur in nature (page 16, bottom).

Thus, the claims are extremely broad. For example, in their broadest embodiments the claims encompass any siRNA targeted to any two RNA messages transcribed by any non-naturally occurring polynucleotide sequences such as any two or more gene fusions as may be found in any recombinant DNA plasmid or vector or in any genetically engineered bacterium, yeast, plant, mouse or non-human mammal. Moreover, the claims broadly embrace any configuration and arrangement of subject and target RNAs, which together constitute the chimeric RNA transcript, such that the universal target may be located upstream or down stream of the subject RNA, or at any position within the subject RNA (see Fig. 1 of the instant application). Indeed, the universal target may be even be found in the untranslated region of the transcript. See also pages 8 and 9 of the specification, which teach that the UtRNA may be of any sequence that facilitates RNAi.

Neither the claims nor the specification adequately describe the structural and/or functional characteristics of a “chimeric RNA transcript” as embraced by the invention and as defined at page 16 of the specification such that one of skill in the art could immediately distinguish a “chimeric RNA transcript” from any other RNA transcript that occurs in nature. That is, the properties and characteristics distinguishing RNA transcripts that do not occur in

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nature from those that do occur in nature are not adequately defined in the instant application such that one of skill would immediately recognize a chimeric RNA transcript as embraced by the claims from any other naturally occurring transcript. As a corollary, one of skill would not therefore recognize Applicants were in possession of the entire genus of chimeric RNA transcripts, and thereby the entire genus of siRNAs and shRNAs targeting said genus. Logically, if the specification has not described the genus of chimeric RNA transcripts, as by describing a sufficient number of species representative of the genus or by describing a structural feature common to the genus, the specification has not adequately described the “universal interfering RNAs” needed to effectively silence, and therefore suppress the expression of the genus of chimeric RNA transcripts required for the instantly claimed kits. Furthermore, neither the claims nor the specification explicitly require that the universal interfering RNA be 100% complementary to the universal target RNA, broadening the scope of the claim even further to include any small interfering RNA that facilitates RNAi to any extent. This would mean that the universal target RNA does not necessarily have to be 100% identical in every transcript as minor mismatches may not preclude the use of a single interfering RNA to target two or more transcripts (see Tuschl et al. US 2004/0259247 A1, paragraph 180, for example).

The broad, generic definition of “chimeric RNA transcript” at page 16, along with the broad definitions of “universal target RNA” and “subject RNA” at pages 16-17 fail to describe any significant distinguishing feature that would allow one of skill in the art to immediately envision the genus of targets now embraced by the claims.

Moreover, the claims are extremely broad, giving rise to substantial confusion as to what may or may not infringe the claimed invention. For example, a chimeric RNA transcript as

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defined at page 16, and as embraced by the instant claims, may include transcripts that differ from wild type, or naturally occurring transcripts by a single nucleotide or a single codon, so long as each of the plurality of transcripts contains a common target sequence and the transcripts as a whole do not occur in nature. Thus, the claims embrace an astronomical number of possible genetic sequences with no clear structural delineation between those that do and do not occur in nature.

The "chimeric RNA transcripts" are essential to the operation/function of the invention, and there is expected to be wide variation in the sequences of such transcripts intended for use in the instant invention.

Neither the instant claims nor the instant application adequately describes the distinguishing structural/functional characteristics of the genus of chimeric RNA transcripts that do not occur in nature such that one of skill in the art could immediately envision the genus apart from all other RNA transcripts that do occur in nature.

For example, neither the claims nor the specification describes any minimum or maximum required length or sequence of the universal target RNA or subject RNA. As a result a chimeric RNA transcript within the scope of the claims may be one that differs from a counterpart wild type gene by only a single nucleotide, a single codon, or by a short sequence in one or more untranslated regions. Further, in the broadest embodiment, any sequence may constitute the universal target. Thus, for example, redundant or consensus sequences in gene families within and across species may be chosen as the UtRNA and the transcript rendered non-natural simply by changing one or a few nucleotides within the consensus sequence in each transcript. In fact, the specification only requires that the transcript not occur in nature, there is

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no prohibition that the protein encoded by the transcript not occur in nature. Thus, even conservative changes in the transcript that do not affect the amino acid sequence would fall within the scope of a chimeric RNA transcript.

Moreover, the prior art taught that single nucleotide polymorphisms, gene transpositions and translocations, viral integration and latency are common. Thus gene rearrangements in nature are commonplace and unpredictable. In view of such occurrences in nature, there is no evidence of record to suggest that one of skill presented with a particular gene sequence would immediately recognize that sequence to be one not naturally found in nature and embraced by the generic definition now recited in the instant claims.

For example, there is not even sufficient disclosure to adequately inform one of skill whether the genus of transcripts found in established cell lines in culture in a laboratory would be considered by the inventors to represent natural or non-natural transcripts, the cell lines having been subjected to handling and non-natural culture conditions in a man-made laboratory, which may or may not alter the genetic characteristics of these cell lines.

Genetic changes, translocations, and alterations occur continually in nature giving rise to RNA transcripts that may or may not have been previously known. The pre- and post-filing art teaches, for example, that gene translocations and expansions may occur in nature and give rise to cancer, neurodegenerative diseases, and possible other disorders in animals (Barr, 1998, *Nature Genetics* 19:121-124; and Reddy et al., 1999 *TINS* 22:248-255, for example). The pre- and post-filing art also teaches that viral genomes may integrate into the genomes of animal host cells and may lie latent for many years (HIV, papilloma virus, and Hepatitis B virus, for

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example). The pre- and post-filing art further teaches the use of gene therapy vectors that may or may not integrate into one or more regions of the host genome.

Aside from the general description that a “chimeric RNA transcript” does not naturally occur in nature, there is no evidence now of record that would enable one of skill at the time of filing to immediately discern the genus of non-naturally occurring transcripts from all other normal and abnormal transcripts found in the animal, plant, and unicellular kingdoms now embraced by the claims.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed (pg. 1117). Because the level of skill and knowledge in the art increases over time, it is essential to determine possession as of the effective filing date.

A disclosure in a parent application that merely renders the later-claimed invention obvious is not sufficient to meet the written description requirement; the disclosure must describe the claimed invention with all its limitations.” (*Tronzo v. Biomet Inc.*, 156 F.3d 1154, 1158, 47 USPQ2d 1829, 1832 [Fed. Cir. 1998]). The specification need not, however, describe the claimed invention using the same words as the claims (*Purdue Pharma L.P. v. Faulding, Inc.*, 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 [Fed. Cir. 2000]).

In the instant case, the specification does not clearly allow persons of ordinary skill in the art to recognize that Applicants invented what is now claimed. The application does not enable the skilled artisan to clearly envision the chemical structure of the encompassed genus of

chimeric RNA transcripts, comprising a universal target RNA and subject RNA, that do not occur in nature.

An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

MPEP §2163 states, in part: “[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated. A patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when … the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed. *In re Curtis*, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004).”

In the instant case, the prior art indicates a degree of variation in the population of chimeric RNA transcripts which may or may not fall within the scope of the claim. Applicants provide neither a representative number of species nor any partial or complete structure of the genus of chimeric RNA transcripts and/or universal target RNAs that would enable one of skill to discern those transcripts that fall within the scope of claims from those that occur in nature and therefore do not infringe the claims.

Accordingly, the instant claims are rejected for lack adequate written description support of the genus of chimeric RNA transcripts, as defined by the specification at page 16.

Applicant is reminded that the written description requirement is separate and distinct from the enablement requirement. *In re Barker*, 559 F.2d 588, 194 USPQ 470 (CCPA 1977), cert. denied, 434 U.S. 1064 (1978); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1115 (Fed. Cir. 1991).

Claim Rejections - 35 USC § 101—withdrawn

The rejection of Claims 18–20, 24–26, and 31–34 under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter is withdrawn in view of Applicants' amendments to the claims.

Claim Rejections - 35 USC § 101—new

Claims 16–34 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial utility or a well established utility. According to the Revised Utility Examination Guidelines, see the Federal Register, Vol. 66, No. 4, pp. 19092-1099 (January 5, 2001), also available at <http://www.uspto.gov/web/menu/utility.pdf> the following definitions of credible, specific, and substantial apply.

A credible utility is one that a person of ordinary skill in the art would accept as currently available. An assertion is considered credible unless (a) the logic underlying the assertion is seriously flawed, or (b) the facts upon which the assertion is based are inconsistent with the logic underlying the assertion. Credibility as used in this context refers to the reliability of the statement based on the logic and facts that are offered by the Applicant to support the assertion

of utility. A credible utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for such use.

A specific utility is one that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention.

A substantial utility is one that defines a real world use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a real world context of use are not substantial utilities. Research that involves studying the properties of the claimed product itself does not constitute a substantial utility.

See also MPEP 2107-2107.02, and *Brenner, Comr. Pats. v. Manson*, 148 USPQ 689 (US SupCt 1966).

The instant claims are drawn to kits comprising a plurality of vectors, cells, and transgenic organisms, including any non-human mammal, that express chimeric (non-naturally occurring) RNA transcripts, composed of a subject RNA linked to a universal target RNA, and a universal interfering RNA targeting said universal target.

The specification identifies the following uses for the claimed kits, and thereby, vectors, cells, and organisms: 1) investigating gene function and 2) treating disease. Moreover, these utilities are interrelated and overlapping as the investigation of gene function can take several forms such as correlating gene expression with disease phenotype, verifying drug targets, and developing new or improved treatment protocols. The underlying assumption of these utilites taught by the instant specification seems to be that, in general, the biological properties and activities of an expressed chimeric RNA transcript will mimic the molecular biological activities of the natural or wild-type subject RNA contained in that chimeric RNA transcript thereby

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providing insight as to the function of that subject RNA *in vitro* and *in vivo*. In embodiments involving knockouts and transgenic organisms, the underlying assumption seems to be that expression of a chimeric RNA transcript will replace and/or restore the biological disease-preventing or disease-causing phenotype of the subject RNA, or perhaps that the over-expression of a chimeric RNA transcript will yield some practical real-world information with regard to natural gene function and disease. In other words, the assumption appears to be that non-naturally occurring chimeric RNA transcripts are functionally equivalent to the subject RNA contained therein. However, there is no evidence to substantiate any of these assumptions either in the specification or the prior art.

In regards to asserted utility 1), the stated utility of the expression vectors, cells, and non-human organisms and corresponding universal siRNAs for investigating gene function *in vitro* or *in vivo* in a high throughput manner, does not constitute a real world utility and therefore is not a substantial utility, but rather represents further research on the product to identify or reasonably confirm a real world utility. In essence, the asserted utility represents an invitation to experiment using the claimed kits to screen for and identify phenotypes associated with the expression of chimeric RNA transcripts without any assurance that any practical phenotype or disease model of currently available, real world value will ever emerge or be identified.

As stated in the USPTO Utility Guidelines, research that involves studying the properties of the claimed product itself does not constitute a substantial utility. Further, such an asserted utility constitutes a general, rather than a specific utility, as any chimeric RNA transcript and corresponding UiRNA thereof can be used to study the effects of the loss of function of *that* transcript, with the assumption that some correlation may exist between the loss of that

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transcript, a non-natural transcript, and a disease. Such an assumption amounts to conjecture and speculation at best as not even a single representative example showing correlation between the expression of a non-naturally occurring transcript and disease or gene function has been provided.

Moreover, the overexpression of any non-naturally occurring chimeric RNA transcript may lead to some phenotype in cell or organism. Whether that overexpression has any connection to a natural phenomenon or would yield any information of immediately available, real-world value is a separate inquiry altogether. There is no evidence of record to show that any such phenotype derived from the under or overexpression of a non-naturally occurring chimeric RNA transcript within the scope of the claims may be readily correlated to any specific disease or may serve as a recognized model for the study of the function of a subject RNA. Therefore, asserted utility 1) does not meet the standard for a specific and substantial utility.

In regards to asserted utility 2), as identified above, the specification fails to demonstrate that any cell or non-human organism comprising any of the plurality of expression vectors or chimeric RNA transcripts now recited in the instant claims would have any phenotype associated with any disease, or can in fact be used as a model for any particular disease. The specification generally states that “The transfected target cells or organisms can then be examined in the presence and absence of such UiRNAs, to determine whether the gene product whose expression level is being manipulated by RNAi, does indeed play a role in pathogenesis, genetic disorders, or infectious diseases” (page 12, for example); however, neither the specification nor the prior art specifically identifies any phenotype in any cell or organism, plant or animal, caused by the normal or abnormal expression of any non-naturally occurring chimeric RNA transcript, or

provide any correlation or representative example of how any such phenotype caused by the expression of a non-naturally occurring RNA transcript may reasonably correlate to any specific disease caused by any counterpart wild-type or natural gene.

In certain embodiments, the specification teaches making knockouts (presumably homozygous) for use with the instant kits to identify phenotypes associated with the expression of any chimeric RNA transcript (page 56). In other embodiments, the specification teaches that simply overexpressing a chimeric RNA transcript may lead to a phenotypic change. However, in neither case does the specification teach the correlation of any specific disease and the expression of any chimeric RNA transcript, or provide any representative examples teaching or showing that any practical real world abnormality or phenotype was in fact identified by the knockdown of any chimeric RNA transcript within the scope of the instant claims.

As such, the specification fails to teach any specific phenotype associated with gene disruption and/or chimeric RNA expression in any cell or organism. Thus, in the absence of any specific teachings as to actual phenotypes or diseases associated with the instantly recited chimeric RNA transcripts and universal interfering RNAs, the asserted utilities of investigating gene function in disease is neither specific nor substantial as it would require further research to identify a disease associated with the expression of a chimeric RNA transcript, if any exist, and to correlate any observed phenotype or characteristics with the characteristics of a particular disease.

Even supposing that any given chimeric RNA transcript would serve as a functional equivalent of the corresponding subject RNA, the loss of a gene altogether, and thereby the replacement of that gene, as by a chimeric RNA expression, may not necessarily produce any

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identifiable phenotype, reducing one of skill to a hunting expedition to find and identify chimeric RNA transcripts having a specific substantial utility. Alternatively, the loss of a gene and/or addition of a chimeric RNA transcript may produce a complex array of phenotypes or even render the cell or organism non-viable, preventing any identification of or correlation to a specific function for the subject RNA of any real world value.

Thus, the proposed use of the recited chimeric RNA transcripts and universal interfering RNAs for investigating gene function and identifying therapeutic targets are simply starting points for further research and investigation into potential practical uses of the claimed kits. *See, Brenner v. Manson*, 148 U.S.P.Q. 689 (U.S. 1966), wherein the court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Thus, in view of the discussion above, the skilled artisan would not find any of the asserted utilities of the expression vectors, cells, and organisms comprising and expressing the recited chimeric RNA transcripts encompassed by the claims to be specific and substantial, or well-established.

Claim Rejections - 35 USC § 112, first Paragraph—new

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16-34 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 18–34 are further rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for the reasons set forth below. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in a determination of lack of enablement include, but are not limited to:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and

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(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

The claims are drawn to kits comprising a plurality of non-human organisms each expressing a different chimeric RNA transcript. The claim language in conjunction with the intended uses taught in the instant application involving the manufacture of transgenic organisms expressing said transcripts for the study of gene function and disease, requires that the instant claims be evaluated to ensure enabling support is present to make and use the full scope of the invention now claimed.

The invention is in a class of invention that the CAFC has characterized as “the unpredictable arts such as chemistry and biology.” *Mycogen Plant Sci., Inc. v Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001) since the claimed kits require one of skill in the art to make and use transgenic organisms

The claims are very broad. For instance, in their broadest embodiments, the claims encompass kits comprising libraries of genetically distinct non-human transgenic organisms of any species, plant or animal, expressing non-naturally occurring chimeric RNA transcripts. The specification explicitly contemplates using the instant kits to investigate gene function and study disease.

Accordingly, the instant claims require the manufacture and use of a “plurality” of any non-human transgenic organisms expressing distinct chimeric RNA transcripts, wherein the chimeric transcript is composed of a subject RNA and a universal target RNA. The specification

teaches generally that cleaving the chimeric RNA transcript within the target RNA will inhibit the translation and function of the subject RNA, thereby yielding information as to the function of that gene. This utility requires making and using cells and organisms expressing said transcripts, and in some cases eliminating wild type, naturally occurring genes to remove redundancy and eliminate activities that may mask the function of the chimeric RNA transcript. The specification teaches that in general transgenic organisms and cells expressing non-naturally occurring chimeric RNA transcripts are useful for studying gene function and disease.

Enabling support does not exist for making and using the full scope of non-human organisms embraced by the claims. Neither the specification nor the prior art taught one of skill how to make and use the genus of non-human organisms now required expressing non-naturally occurring chimeric RNA transcripts for the study of gene function and disease. The prior art indicates that, with the exception of mice, making and using transgenic and knockout animals was not well established and required undue experimentation. The prior art further indicates that making and using knockout and transgenic mice having predictable phenotypes and genotypes was unpredictable and required undue experimentation. Thus, the prior art suggests that the phenotypes of genetically engineered animals is complex and unpredictable.

Knowledge of a specific genotype and phenotype is required before the claimed organism could be used for the analysis of gene function or disease. Moreover, in some embodiments, using the claimed kits requires the use of specific and selective knockout animals and plants to properly identify the function of any chimeric transcript gene. Neither the instant application nor the prior art provides disclosure that would reasonably enable one of skill to make and use the complete genus of knockout animals. Rather the prior suggests that knockout and transgenic technology was enabled only for mice, and that even with mice the phenotype obtained was unpredictable.

While the prior art taught and enabled the use of transitive RNAi as means to inhibit neighboring genes in certain organisms, neither the prior art nor the instant application provide any representative examples or guidance showing how to make and use the genus of non-human organisms each expressing chimeric RNA transcripts to study gene function and disease *in vivo*. The specification does not disclose or claim any animal or plant with any specific disease or family of disorders relating to the expression of any chimeric RNA transcript

Currently, the production of transgenic animals depends on the use of embryonic stem (ES) cells, and this technology is well developed only in the mouse system. The state of the art with respect to the use of ES cells from other organisms is set forth by Mullins et al. (1996) *J. Clin. Invest.* 98(11), Supplement S37-S40 who teach that techniques for the use of non-mouse ES cells are based on those developed for mouse ES cells, and that these techniques are in need of further refinement (pages 37 and 38). Specifically, chimeric non-mouse animals have been created by the injection into blastocysts of freshly isolated ES cells, and totipotency of these cells has been demonstrated. However, attempts to culture non-mouse ES cells result in differentiation

and loss of totipotency. Culturing of ES cells is essential for the selection process required in the instant invention. Therefore the state of the art for the production of non-mouse animals encompassed by the claims is highly unpredictable. Furthermore, the specification offers no guidance in this respect, and in the cases of non-human primates and chimpanzees there are no transgenic examples in the art. It is noted that the production of transgenic animals by other techniques such as pronuclear microinjection is well established. However, these techniques are labor intensive compared to the ES cell approach, and generally result in the insertion of concatenated sequences. The specification discloses a technique which gives rise to single insertion events (transfection of ES cells), and does not teach how concatenated inserts would affect the invention. Thus, in view of the breadth of the claims, the lack of predictability of the art, and the lack of guidance in the specification, a skilled artisan would be required to perform undue experimentation without reasonable expectation of success in order to produce non-mouse versions of the claimed organisms.

With respect to making knockout animals of all species, Bradley et al. (1992) *Biotechnology* 10: 534-539 set forth the state of the art with respect to ES cells for species other than mice and the unpredictability of non-human ES cells other than mice ES cells giving rise to somatic and germ cells. Bradley *et al* disclose that at that time, there were no ES cells for any animal other than a mouse which had been established to give rise to somatic tissues or germ cells *in vivo*. The claims encompass the introduction of a transgene into an ES cell, and if ES cells of all animal species other than a mouse have not been established at the time of filing, the production of transgenic non-human animals (via ES cell technology) of all species other than a mouse is unpredictable if not virtually impossible. Thus, it is unpredictable whether the one

could employ current methods to produce the transgenic non-human, non-mouse mammals which are encompassed by the claims.

In addition, the art did not consider the correlation between any observed mouse phenotypes and human disease phenotypes as predictable. Doetschmann et al. teaches that “[o]ne often hears the comment that genetically engineered mice, especially knockout mice, are not useful because they frequently do not yield the expected phenotype, or they don’t seem to have any phenotype” (Doetschmann (1999) Lab. Animal Sci., Vol. 49 (2), 137-143, see page 137, column 1, paragraph 1). Doetschmann provides numerous examples of instances in which genes considered well-characterized *in vitro* have produced unexpected phenotypes or indiscernible or no phenotypes in transgenic or knockout mice.

Moens et al. further teaches that different mutations in the same gene can lead to unexpected differences in the phenotype observed. Moens et al. shows that two mutations produced by homologous recombination in two different locations of the N-myc gene produce two different phenotypes in mouse embryonic stem cells, one leaky and one null (Moens et al. (1993) Development, Vol. 199, 485-499).

Further, the art demonstrates the unpredictability of making a mouse model for human disease by disrupting the murine gene. Jacks et al. teaches that although retinoblastoma (Rb) gene mutations in humans are associated with retinal tumors, Rb gene knockout mice had tumors in the pituitary gland rather than the retinas (Jacks et al. (1992) Nature, Vol. 359, 295-300).

Thus, the art at the time of filing clearly establishes the unpredictability of determining the phenotype of a transgenic organism or knockout mouse even when the activity of the gene

has been extensively studied *in vitro*, and further establishes the unpredictability of generating a mouse model for human disease based on the activity of the gene in humans.

The specification provides adequate guidance as to how to make a chimeric RNA transcript and expression vector thereof, but the specification provides no guidance as to how to make an animal with any specific phenotype or genotype. The specification provides no guidance as to how to use an animal with no specific phenotype or genotype. The claims recite no specific genotype or phenotype. As discussed above, in the absence of a specific phenotype and genotype, no meaningful correlation can be made between the gene into which the vector is inserted and any specific disease or physiological characteristic. As a result, the phenotype and genotype of a transgenic animal intended to be used for the study of the relationship between genes and physiology must be considered to be a critical element of the invention.

In Genentech, Inc, v Novo Nordisk A/S, the court found that when the specification omits any specific starting material required to practice an invention, or the conditions under which a process can be carried out, there is a failure to meet the enablement requirement. See 42 USPQ2d 1001.

It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

In this case, the identification of a mouse or any other animal with a specific genotype or phenotype cannot be considered a minor detail which can be omitted in the process of providing an enabling disclosure.

One of skill in the art at the time of the invention would have had to perform undue experimentation in order to use the claimed non-human organisms as intended to study gene function or disease because the claimed animals have no phenotype or genotype which one could correlate with any aspect of physiology or disease. As indicated above, even if the specification disclosed a specific gene into which an insertion mutation was to be directed, the phenotype and usefulness of the resulting animal would be highly unpredictable. In the instant claims, no phenotype or genotype is recited, therefore the unpredictability associated with using the claimed organisms is even greater than that normally associated with targeted insertional mutations, such that one of skill in the art could not use the claimed invention as intended.

Thus, considering the breadth of the claims, the state of the art at the time of filing, the level of unpredictability in the art, and the limited guidance and working examples provided by the instant application, the Examiner submits that the skilled artisan would be required to conduct undue, trial and error experimentation to practice the claimed invention commensurate with the claims scope.

Accordingly, the instant claims are rejected for failing to comply with the enablement requirement.

Claim Rejections - 35 USC § 103—withdrawn

The rejection of Claims 21–26 under 35 U.S.C. 103(a) as being unpatentable over Sijen et al. (2001) *Cell* 107:465–476; Pal-Bhadra et al. (1998) *Cell* 99: 35–46; Voinnet et al. (1998)

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Cell 95:177–187; Fire et al. (1990) *Gene* 93:189–198; Kennerdell et al. (1998) *Cell* 95:1017–1026; and Elbashir et al. (2001) *Nature* 411:494-498 upon further consideration in view of Applicant's arguments, which are deemed persuasive in part.

Specifically, while the instant references taught and/or suggested the study of transitive RNAi in mammalian and non-mammalian organisms using artificial gene constructs and siRNA, the combination of references does not explicitly or implicitly teach or suggest using multiple, i.e., 10 or more, such constructs in any transitive RNAi study, as required by claims 21–26. Further it does not appear that one of skill would ordinarily require or use several different constructs (i.e., 100 or more) in any investigation of transitive RNAi.

Claim Rejections - 35 USC § 103—maintained

Claims 16–20 and 27–34 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Sijen et al. (2001) *Cell* 107:465–476; Pal-Bhadra et al. (1998) *Cell* 99: 35–46; Voinnet et al. (1998) *Cell* 95:177–187; Fire et al. (1990) *Gene* 93:189–198; Kennerdell et al. (1998) *Cell* 95:1017-1026; and Elbashir et al. (2001) *Nature* 411:494-498.

The claims are drawn to a kit comprising a plurality of expression vectors, cells, or organisms, each comprising an expression cassette that directs the expression of a chimeric RNA transcript that has a subject RNA operably linked to a universal target RNA, wherein at least two of the plurality of expression vectors, cells, or organisms express chimeric RNA transcripts with different subject RNAs, and wherein all of said plurality of expression vectors, cells, or organisms express chimeric RNA transcripts with the same universal target RNA; and a universal interfering RNA targeting said universal target RNA, or an interfering RNA

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transcription vector that directs the expression of said universal interfering RNA, wherein said universal interfering RNA is an siRNA or shRNA.

The specification defines a “chimeric RNA transcript” as an RNA transcript comprising a subject RNA operably linked to a universal target RNA to create a single RNA that does not naturally occur in nature (page 16, bottom).

Sijen et al. teach materials and methods for investigating transitive RNAi and gene function in *C. elegans*, comprising the use of transgenic *C. elegans* organisms and vectors expressing chimeric GFP-encoding transcripts (see Fig. 3). A proposed model for transitive RNAi is presented in Fig. 1. The authors teach that the model leads to a number of testable predictions, wherein an initial trigger dsRNA targeted to one region of an mRNA will lead to the production of secondary dsRNAs directed to other, possibly, upstream regions of the same or homologous target RNA (page 466). This is schematically depicted in Fig. 1B and 1C.

To compile direct evidence for transitive RNAi, Sijen et al. constructed two different vectors: the first expressing GFP fused to lacZ; the second, GFP alone (Fig. 3). In the first vector, the GFP gene is further fused to a nuclear location signal (NLS), while in the second vector GFP is further fused to a mitochondrial location signal (Mito). Using dsRNA targeted to the lacZ region, Sijen et al. show that lacZ-specific dsRNA inhibited the expression of GFP in both the mitochondrially targeted and nuclear targeted transcripts, indicating that a single dsRNA trigger directed to a downstream sequence could inhibit the expression of two different transcripts. The result is attributed to the production of secondary RNAi against the upstream sequence, GFP, induced or triggered by a single dsRNA targeting the downstream sequence, lacZ (Fig. 3, page 468).

As further proof of transitive RNAi, Sijen et al. created transgenic nematodes comprising an *unc-22::gfp* transgene. Sijen et al. then show that injection of GFP-specific dsRNA into wild-type animals produced no phenotype, whereas injection of GFP-specific dsRNA into transgenic animals expressing an *unc-22::gfp* transgene produced a twitching phenotype characteristic of inhibition of *unc-22* (Fig. 4C, and page 468, left column, bottom). The results provide further evidence of transitive RNAi in *C. elegans*. Further tests with in-frame deletion mutants provide yet further evidence for transitive RNAi, and lead Sijen et al. to state at page 468, right column, that these experiments demonstrate that transitive RNAi is not limited to transgene targets, but can also target physiological expression of cellular genes.

Altogether then, Sijen et al. demonstrate how a single interfering dsRNA can inhibit the expression of at least three different, non-naturally occurring transcripts, and at least two different subject RNAs linked to a common target, GFP. In this case, Sijen et al. show and implicitly suggest that linking a common, non-naturally occurring sequence such as GFP or lacZ, to different genes, such as *unc-22* and GFP, can render such sequences susceptible to RNAi via a single dsRNA targeted to the GFP or any other down stream sequence. The tests were designed to study the transitive RNAi phenomenon in *C. elegans*, but Sijen et al. suggest implicitly and explicitly that similar studies might be carried out to further elucidate the biochemical mechanisms of transitive RNAi in *C. elegans* as well as other organisms, including *Drosophila* and plants. For instance, Sijen et al. state that the absence of an identified RdRP homolog in *Drosophila* and mammals suggests either (1) that other RNA copying enzymes are used in these systems for amplification or (2) that the primary siRNAs may be sufficient to produce detectable interference response (page 473 bridging to 474).

Sijen et al. state further, at page 474, left column, that “With or without an RNA copying process, a variety of additional amplification mechanisms may contribute to silencing. In this regard, it is of interest to note two previous examples of transitive silencing: Pal-Bhadra et al. observed examples of transitive silencing in *Drosophila*, while Voinnet et al. reported transitive silencing with a GFP transgene target in plants.” “It will be of interest in the future to understand the breadth of different amplification events operating in gene silencing and their biological roles.”

Thus, Sijen et al. clearly suggest further studies of transitive RNAi in other organisms as well as in *C. elegans*.

Importantly, Sijen et al. also explicitly recognize the value and utility of siRNAs for these types of studies. At page 471, for example, Sijen et al. teach that siRNAs (21-25 nt) may be used effectively in *C. elegans* to specifically reduce the expression of certain target genes (page 471), for example, to study the function of certain genes and their role in transitive RNAi. Sijen et al. explicitly refer to the teachings of Elbashir et al. regarding the material description and function of siRNAs in general (page 471).

Sijen et al. conclude by stating that “A number of extant models for gene silencing in plants propose an amplification step relying on chromosome-targeted effects.” “It will be of interest in the future to understand the breadth of different amplification events operating in gene silencing and their biological roles” (page 474).

While Sijen et al. teach vectors and organisms comprising at least two different non-naturally occurring transcripts (unc-22::GFP and pSAK2, GFP-lacZ and pSAK4, GFP) and methods for silencing different non-homologous targets using interfering dsRNA directed to a

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non-homologous down stream sequence operably linked to the non-homologous target, and while these experiments clearly suggest that one dsRNA can silence multiple different upstream targets linked to the same down stream target, Sijen et al. do not explicitly teach at least two different vectors or transgenic organisms in a single array or single experiment comprising at least two different subject RNAs linked to the same target, downstream sequence such as GFP or lacZ.

Fire et al. disclose a modular set of *lacZ* fusion vectors for studying gene expression in *Caenorhabditis elegans*. It is taught and shown that the vectors enable one to analyze the expression of several genes in the nematode *C. elegans*. It is taught that *lacZ* can be expressed in wide variety of different tissues and cell types, and that these vectors should be useful in studying gene expression both in *C. elegans* and other experimental systems. In particular, it is taught that the *lacZ* encoded enzyme, β -galactosidase, serves as a sensitive and reliable reporter for monitoring the expression of any fusion.

Fire et al. provide a detailed description of the materials and methods used to construct and manipulate the vectors for purposes of cloning and expression under a variety of conditions and in a range of different cell types and subcellular locations.

Accordingly, Fire et al. implicitly and explicitly suggest a wide variety possible uses for the vectors and libraries that have been and may be constructed with them.

Kennedell et al. teach that dsRNA interference may be a valuable system with which to understand aspects of gene function in many organisms (page 1018). Using RNAi to study gene function in *Drosophila*. Kennerdell et al. teach that a sequence shared between several closely related genes may interfere with several members of the same family. For example, Kennerdell et al. state that dsRNAs corresponding to the 5' UTRs of *fz* and *Dfz2* had no interfering activities

on their own, but dsRNAs corresponding to coding sequences shared by *fz* and *Dfz2* had weak but significant interfering activities (page 1022).

Kennerdell et al., therefore, imply that double-stranded, interfering RNA targeted to a single common sequence can inhibit the expression and function of more than one gene comprising that common sequence.

Kennerdell et al. teach that the mechanism of dsRNA interference is unknown, and if the mechanism is the same for flies and nematodes, then work from *C. elegans* points to a post-transcriptional mechanism (page 1023, left, top). Kennerdell et al. speculate that interference may involve an amplification step (page 1023). Therefore, Kennerdell et al. implicitly suggest further studies to investigate possible amplification mechanisms in these and other organisms.

Elbashir et al. teach the advantages, synthesis, and use of siRNAs in general for mediating gene-specific inhibition in flies and mammalian cells. Elbashir et al. teach in general that RNAi is an effective tool for studying gene function.

It would have been obvious to one of skill in the art at the time the instant invention was made to make and use vectors, cells, and transgenic organisms expressing different genes fused to a common reporter sequence or sequences such as *lacZ* and/or *gfp*, to study transitive RNAi in *C. elegans* and other organisms including *Drosophila* and plants, as suggested by Kennerdell et al. and Sijen et al. It would further have been obvious to make and use several different chimeric vectors, transgenic organisms and/or host cells, to define and elucidate transitive RNAi and/or amplification mechanisms in a variety of organisms. As part of the overall study, it would have been standard laboratory practice to produce and test several different expression constructs and/or organisms in compartments, such as 96-well plates, racks of test tubes, multi-well culture

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plates and or petri-dishes, depending on the experiment and organism, and as part of the overall design choice.

>Furthermore, in any well designed experiment, it would have been obvious, indeed necessary, to include both positive and negative controls. Thus, any experiment designed to test the existence of transitive RNAi in a mammalian cell using reporter gene constructs would necessarily include siRNA and dsRNA controls targeted to the reporter gene sequence (i.e., the common or universal sequence) to verify the RNAi competency of the test system.<

One would have been well motivated given that both Sijen et al. and Kennerdell et al. emphasize the importance of the amplification effect and possible systemic spread of RNAi in some organisms. One of skill in the art would have been motivated to define these mechanisms and more clearly understand the role it plays in naturally occurring RNAi, as part of viral defense, for example in plants and/or higher eukaryotes. One would have been motivated to make and test several different configurations of transgenes and vectors encoding chimeric transcripts, and to arrange such constructs in an organized fashion, compartmentalized as per normal laboratory practice, in well-marked containers, wells, test tubes, microtiter plates and so on, to define the particular molecular requirements of transitive RNAi in any given organism. Thus several hundred if not thousands of possible configurations and conditions would be provided for study.

One would have had a reasonable expectation of success given that Fire et al. show how to clone and express hundreds of genes of different genes as fusions to *lacZ*, a well defined and easily visualized reporter gene, against which interfering RNAs are easily prepared and readily available. Alternatively or in addition, one of skill would have had easy access to GFP encoding

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constructs and would have known how to manipulate and construct many different GFP encoding constructs for studying transitive RNAi, based on the teachings and exemplary embodiments given in Sijen et al., Par-Bhadra et al., and Voinnet et al., and as suggested by Kennerdell et al.

Accordingly, the Examiner submits that the instant invention would have been *prima facie* obvious to one of skill in the art at the time the invention was made.

Response to Arguments

Pages 10–23 of Applicant's arguments filed 3/22/07 have been fully considered but they are not persuasive.

Applicant argues the references neither taught nor suggested a universal interfering RNA, that the Examiner has failed to identify where such a universal interfering RNA is specifically taught or suggested, and that the Examiner has failed to set forth "the difference or differences in the claim over the applied references (page 13).

These arguments are unpersuasive because although the combination of references never use the term "universal interfering RNA," a term coined by applicant, the references teach and suggest interfering RNAs, both long and short, targeted to common sequences in different transcripts for the study of transitive RNAi in mammalian cells *in vitro* and *in vivo*. Elbashir et al. provide the suggestion to use siRNAs (in place of long dsRNAs) in mammalian cells to avoid the interferon response. One of skill would have known this at the time of invention, and would have selected siRNAs for transitive RNAi studies in mammalian cells to avoid such non-specific effects. Second, it is common knowledge and normal practice in the chemical and biological arts

to include both positive and negative controls in any well designed experiment. In the instant case, the combination of references suggests screening for the presence or existence of transitive RNAi in mammalian cells and organisms using recombinantly engineered vectors and nematodes expressing reporter genes linked to one or more additional genes that produce a detectable phenotype upon inhibition of expression. One of skill would have included as a positive control siRNAs directed to the commonly expressed sequence to verify the RNAi competency of the assay system. The use of controls is implied. Nevertheless, for clarity, an explicit statement to this effect has been added to the rejection, reiterated in full above.

As to Applicants assertion that the differences between the primary reference and the claims are not laid out in the rejection, the Examiner disagrees. Applicant is referred to the top of page 8 of the non-final rejection, which discusses the differences between Sijen et al. and the instant claims.

Applicants assert that the instant claims have broader application than defining transitive RNAi, and that the Examiner's assertion that motivation to combine for the study of transitive RNAi is not relevant to the problem to be solved by the invention (page 15). This argument is not persuasive because the instant claims clearly embrace systems and materials suitable for the study of transitive RNAi. The specification itself makes it clear that transitive RNAi is a recognized application of the instant kits and methods (see Fig. 5 and page 14, legend to Fig. 5). Moreover, it matters not that the claims are broader than the application suggested in the prior art so long as the application suggested by the prior art is embraced by the scope of the instant claims.

At pages 16–23, Applicant argues at length that the references teach away from any combination and that the Examiner has applied hindsight reasoning. Applicant further argues the references individually pointing out alleged deficiencies with regard to claim limitations in each reference.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

It is unnecessary in a rejection under 35 USC §103 that each reference teach and suggest every limitation in the claims. In the instant case, the combination of references teach and suggest siRNAs for the study of transitive RNAi in mammalian systems using two or more reporter gene constructs comprising different genes connected to a common reporter gene. Because transitive RNAi was discovered in organisms before the discovery of siRNA, it is self-evident that these earlier references would not teach siRNA; nevertheless these references suggest using similar reporter gene constructs to test for transitive RNAi in mammalian systems. Elbashir et al. provide the incentive to use siRNAs in place of long dsRNAs in mammalian systems. Accordingly, one of skill would have been compelled to use siRNAs in any screen for transitive RNAi in a mammalian system. The inclusion of positive and negative controls using siRNAs directed to the common reporter gene portion of the constructs would have been a necessary component of any such experiment.

Further the prior art taught each of the elements necessary to study transitive RNAi in virtually any organism, including *C. elegans* (Fire et al.), and mammalian cells. Moreover, there

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is no prohibition against combining old references with new references. One of skill at the time of invention would have known that siRNAs are just as active in nematodes as in mammalian cells (see Hannon, 2002, *Nature* 418:244-251), and driven perhaps by considerations of cost would have selected siRNAs for use in any transitive RNAi experiment in any organism.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

The Examiner submits that motivation existed in the prior art for one of skill to investigate transitive RNAi in a number of different organisms using artificial gene constructs within the scope of the instant claims, and that the inclusion of negative and positive controls in any such experiment would have been a necessary part of any well designed experiment to establish the RNAi competency of the system.

Finally, Applicant appears to suggest that the sheer number of references used in the instant rejection is evidence of non-obviousness. In response to applicant's argument that the examiner has combined an excessive number of references, reliance on a large number of references in a rejection does not, without more, weigh against the obviousness of the claimed invention. See *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991). On the contrary, the references cited herein are evidence of the wealth of guidance and information teaching and

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suggesting the investigation of transitive RNAi in a number of different organisms, including nematodes and mammals. The combination of references provides numerous examples of how artificial constructs comprising reporter genes such as GFP may be used to identify and study transitive RNAi in almost any organism using both long and short interfering RNAs.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louis V. Wollenberger whose telephone number is 571-272-8144. The examiner can normally be reached on M-F, 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on (571)272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LVW
Examiner, Art Unit 1635
May 1, 2007

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SUPERVISORY PATENT EXAMINER